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Book Review

Getting Control of the Cell Cycle Literature

Cell Cycle Control
Edited by Christopher J. Hutchison and David Glover
New York: IRL Press at Oxford University Press. (1995). 304 pp. $105.00, hardcover; $50.00, paperback.

In 1971, Yoshio Masui and Clement Markert discovered that an activity in fully mature Rana pipiens oocytes could be injected into immature oocytes and induce their maturation from prophase of meiosis I to metaphase of meiosis II. They named this factor MPF (maturation promoting factor). In 1988 MPF was purified from Xenopus egg extracts and by 1990 its components had been cloned and identified as complexes of B-type cyclins and a cyclin dependent kinase (CDK) subunit called CDC2. In the six years since, we have discovered that MPF is just one of a large family of cyclin–CDK complexes found in eukaryotic cells that regulate the cell cycle.

The cell cycle is the period from the formation of a cell, through the duplication of its cellular and genetic contents, up until its division into two identical cells. We now know that all phases of the cell cycle (e.g., START, S-phase, M-phase) are regulated by a temporal series of cyclin–CDK complex cascades. What determines which kinases are active, when they are active, and how their activity regulates cell cycle transitions, has been the subject of extensive research since 1988. In fact, a quick glance at the number of papers on cyclins reveals that in the last 3.5 years over 2000 papers on this topic have been published. This excitement and progress in the field of cell cycle research has necessitated the publication of numerous and regular reviews on the cell cycle that have allowed investigators to keep up to date with the primary literature in their own field. However, piecing together all these articles is a challenge, especially for newcomers to the field.

The authors and editors of *Cell Cycle Control* have simplified the challenge by presenting the cell cycle literature through 1993 in an organized, complete, and generally digestible format. The chapters are written by some of the most outstanding scientists in the cell cycle field, most of whom have been studying the cell cycle since the components of MPF were first identified.

Although this ten chapter book contains a chapter on DNA synthesis, and one on development, the book focuses on cyclin–CDK complexes. The "unified theory" presented in the first chapter by Leland Hartwell explains why this is appropriate for a book on the cell cycle. This theory explains that cyclin–CDK complexes are central to the mechanism that controls the cell cycle, because they phosphorylate proteins that are critical for each cell cycle phase. In addition, cyclin–CDK complexes provide a link between cell cycle phase progression and checkpoint systems that monitor the correct completion of each cell cycle phase. This link arises because, when errors such as DNA damage, or defects in the mitotic spindle are detected, checkpoints inhibit cell cycle progression by inhibiting cyclin–CDK complex activities. Thus one cell cycle step is dependent on the next, not because of a product-substrate relationship, but because of regulatory circuits that act through the cyclin–CDK's. All these aspects of cell cycle regulation by cyclin–CDK complexes are discussed clearly and carefully throughout the book.

A large fraction of what is known about the cell cycle is based on research performed in the genetically tractable model organisms Saccharomyces cerevisiae and Schizosaccharomyces pombe. Chapter Two by Steve Reed, Chris Hutchison, and Stuart Macneill explains the features of yeast that make them excellent systems for cell cycle research. In addition, this chapter contains a thoughtful presentation of useful genetic concepts, such as execution points, that are popular in studies involving these organisms. This chapter also touches on the issue of whether research performed in these organisms can be extrapolated to human cells. On the surface these yeasts appear different from human cells. For example, there is nuclear envelope breakdown in human cells, but not in these yeasts. In addition, what appears to be a mitotic spindle forms prematurely during S-phase in S. cerevisiae. So can research performed in yeast be applied to human cells? Although this issue is not immediately confronted at this point in the book, it is addressed in Chapter Five by Gabriele Basi and Guilio Draetta.

These authors take an example from history to make the point that there is conservation of the components of MPF and cell cycle regulation in general across species. MPF was first purified biochemically from Xenopus extracts. It consisted of two proteins, a 32 kDa and a 45 kDa species. Antibodies generated against yeast CDC2 protein cross-reacted with the 32 kDa species. Thus, this component of Xenopus MPF was identical to yeast CDC2p. This collaboration of information and reagents between scientists studying the cell cycle in yeast and in higher organisms has continued since, allowing the field to advance rapidly. There are subtle differences between organisms, however. For example, *CDC2* encodes the only CDK in S. pombe, and *CDC28* encodes the only CDK in S. cerevisiae, but human cells contain a whole family of CDK's (Chapter Six). Nonetheless, general cell cycle regulatory principles have been found to be the same regardless of the organism. Thus, what we learn in yeast can be extrapolated to higher eukaryotes.

Chapter Three by Steve Reed presents what we know about the role of cyclin–CDK complexes in the commitment to the cell cycle in yeast. This cell cycle phase is called START in yeast and the "restriction point" in mammalian cells. S.cerevisiae and mammalian cells that have passed START are unable to prevent entrance into S-phase in response to nutrient deprivation. This chapter discusses which cyclin–CDK complexes regulate

START and how they were discovered. However, it does not discuss which substrates these cyclin–CDK complexes phosphorylate to perform their function at START, presumably because at the time this book was written, the information was not available. However, some of the substrates had been identified in higher eukaryotes, and this is described in Chapter Six, although this is not cross-referenced in the book. Evidence presented in Chapter Six suggests that the G1 cyclins phosphorylate transcription factors that then activate transcription of proteins involved in S-phase. There is now evidence that the same mechanism functions in yeast.

MPF activity is essential to drive cells into mitosis. Our understanding of the genetics of this is presented in Chapter Four by Stuart Macneill and Peter Fantes. Historically, most research in this area has been performed in S. pombe because entrance into mitosis can be scored easily by microscopic examination. Most of what is known about the regulation of the entrance into mitosis is at the level of how cyclin–CDK complexes are regulated. Thus this chapter focuses on the activating and inhibitory phosphorylations on cyclin–CDK complexes, and on which proteins perform these modifications. As expected, homologues of all these important cyclin–CDK regulators have now been cloned in higher eukaryotes such as Xenopus and humans. This is a difficult topic to present in a book that is geared to a general audience because of the extensive knowledge in this complicated area. Thus, this chapter is dense with a clear and thoughtful presentation of experiments that lead to the identification of the proteins that regulate cyclin–CDK complexes, their regulation and their genetic interactions with each other. Although of high quality, the high level of genetic complexity encountered in this chapter will be a challenge to a newcomer to the field. Such readers will be assisted by some of the excellent figures in this chapter, as well as by reading the more abbreviated sections in Chapter Five that cover this subject in higher eukaryotes where there is no genetics and where less is known!

As promised, what is known about the number of cyclin–CDK complexes in higher eukaryotes and their regulation is presented in Chapter Five by Gabriele Basi and Guilio Draetta and in Chapter Six by Jonathon Pines and Tony Hunter. It is here that we learn that, in contrast to yeast, higher eukaryotes contain more than one CDK subunit, but, like yeast, contain multiple cyclins. This chapter describes how these CDKs and cyclins were discovered, their roles in different aspects of the cell cycle, and how they are regulated. Some of the figures in these chapters are very useful, for example, the figures that align the different cyclins and CDKs from different organisms allow one to quickly assess the amino acids that are conserved between the species. Chapter 5 also describes the predicted crystal structure of CDC2p. This structural prediction was based on the crystal structure of another kinase, cAMP-dependent protein kinase. Since the book was written, the crystal structure of CDK2 and CDK2 in complex with cyclin A has been resolved, showing the predicted structure to be largely correct. As discussed in the book, these structures have allowed us to identify a structural basis for the regulatory effects of phosphorylations and cyclin binding on CDK structure.

The rest of the book is devoted less to cyclin–CDK regulation, and more to the biology of the cell cycle. It includes four chapters, one by Zetterberg and Larsson on microscopic observations of the cell cycle, one on DNA synthesis by Julian Blow, one on cell cycle molecules altered in cancer cells by Emma Lees and Ed Harlow, and one on development and the cell cycle by Helen White-Cooper and David Glover. Thus, armed with the basics of the cell cycle, the reader is now able to tackle these larger issues.

In their chapter (Eight), Zetterberg and Larsson present some of their studies using time-lapse video microscopy to determine the response of single cells in a logarithmically growing population to various treatments. This chapter is extremely thought-provoking. Zetterberg and Larsson's unique approach reveals subtleties of the cell cycle that may be lost in experiments that monitor the average behavior of a population of synchronized cells. For example, these authors were able to determine that there was a restriction point in cells, and when this occurred relative to cytokinesis, simply by monitoring the effects of nutrient deprivation on the cell cycle length of logarithmically growing cells. Unfortunately, however, the authors were unable to go into sufficient detail to facilitate an easy understanding of the experiments and to explain the figures. Thus scientists new to the field might have to refer to the original papers by this author to get a full understanding of the work. Sadly, this chapter was not integrated into the rest of the book. Thus in discussing experiments where, for example, effects on the restriction point are observed, there is no mention of what might be happening to the cyclin–CDK complexes that are acting at this time. Instead the reader should refer to a more recent review by the same author that was published with this exact goal in mind. Nonetheless this is an important and interesting chapter.

Molecules such as cyclin–CDK complexes that have the potential to regulate growth might naturally be expected to be mutated in cancer cells. Chapter Nine by Emma Lees and Ed Harlow discusses this topic and shows that that is in fact true. For example, mutations in the mammalian G1 cyclin, cyclinD, were some of the first alterations of cyclin–CDK complexes and their regulators that were found in cancer cells.

The final chapter of the book discusses the fascinating topic of the role of cell cycle regulation during development in Drosophila. This is a difficult topic to present in one chapter in a book with no other developmental biology or Drosophila biology, because these topics require extensive introduction. Probably because of this, and in contrast to the reasonably basic level of the rest of the book, this topic is presented at a level that is readily accessible only to scientists familiar with Drosophila genetics and developmental biology. The figures do not help much either. They are extremely useful to experts in the cell cycle field who need to be reminded of the details of the early Drosophila cell cycle. However, scientists new to this area might find the brevity of the legends disappointing. Thus, this chapter will be interesting to the Drosophila experts and developmentally sophisticated, but for the rest it will serve as a means to

identify tantalizing areas of research, and the references with which to understand them.

This book provides a wealth of information concerning the number of cyclin–CDK complexes, when they are required in the cell cycle, and how these complexes are regulated. Sadly, despite the fact that the "unified theory" states that cyclin–CDK complexes regulate the cell cycle by *phosphorylating key substrates*, the authors have correctly devoted very little space to the substrates that are modified. The extent of their discussion of cyclin–CDK substrates in Chapters One and Five is a correct reflection of the extent of our knowledge of this area. The reason for this lack of information is mentioned by Leland Hartwell in the beginning of the book: it is difficult to prove whether a kinase phosphorylates a substrate directly or indirectly, and whether this modification is significant to the substrate's function in vivo. Hopefully this void in our knowledge about cell cycle regulation will soon be filled.

An important issue can be raised about books on the cell cycle in general. Can they be published fast enough to be current, or should we simply rely on reviews published in scientific journals? *Cell Cycle Control* provides an example of the type of book on the cell cycle that is very useful. Although most of the references in this book are from 1993, and the book was published a year ago, in 1996, the book is excellent, and is definitely worth purchasing. This book will rapidly, and without hours of photocopying, bring one up to date with the history, methods, organisms, jargon, and thinking prevalent in the cell cycle field. It will provide scientists with an excellent reference list of key papers in the field that should be studied. In addition, it will provide a number of very useful figures that are the result of compiling a number of different papers. Finally, although this book will only bring scientists up to date with experiments performed up until 1994, because of the high scientific quality of the authors, there was no overinterpretation of data, and therefore no conclusions or predictions that have since been shown to be wrong. *Cell Cycle Control* thus provides readers with a strong foundation with which to tackle papers and reviews published since the beginning of 1994. However, it is always better if a book can be published faster and perhaps books in such a rapidly advancing field should only be published by publishers that can publish rapidly.

Overall, this book is recommended and highly so for those who want a jump start into the cell cycle field. It provides a thorough and thoughtful introduction to the cell cycle with specific emphasis on the regulation of cyclin–CDK complexes. Generally the figures are extremely useful and clear. As with any multi-author book, there is some redundancy. However, given the complexity of the field, the redundancy may prove useful to the novice who might have a hard time keeping track of all the cell cycle players. The book is written for the scientifically sophisticated reader. Its presentation is at the level of discussing the key experiments in a scientific paper, without explaining the techniques. Certainly a post-doc or senior graduate student that is coming from a different background will benefit tremendously from this book.

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